## Proposed EC/sub-subclass

2.7.11.22

## Accepted name

Cyclin-dependent kinase 5

## Synonyms

CDK5; p35/p39-activated serine/threonine kinase

## Phylogeny

CDK5 is an evolutionarily ancient member of the CDK family that clusters separately from classical cell-cycle CDKs. Sequence homology with the yeast kinase Pho85 and the presence of orthologues across metazoans indicate an early metazoan origin and strong conservation throughout mammalian species (Malumbres, 2014; Su & Tsai, 2011). Unlike other CDKs, CDK5 employs neuron-specific activators (p35, p39) instead of canonical cyclins, reflecting a branch that specialised for neuronal signalling rather than cell-cycle control (Łukasik et al., 2021).

## Reaction catalysed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Shukla & Singh, 2020).

## Cofactor requirements

Mg²⁺ is essential for catalytic activity (Malumbres, 2014).

## Specificity

CDK5 is a proline-directed Ser/Thr kinase that favours motifs in which the phospho-acceptor residue is followed by Pro; optimal sites conform to S/TPXK/R (Sharma et al., 1999). Substrate choice is further tuned by binding to p35 or p39, directing phosphorylation toward neuronal proteins such as tau, neurofilaments, MAP1B/MAP2 and other cytoskeletal or synaptic regulators (Dhariwala & Rajadhyaksha, 2008; Cheung & Ip, 2012). Basic residues near the +3 position enhance recognition.

## Structure

The kinase adopts the canonical bilobed fold: a β-sheet-rich N-lobe and an α-helical C-lobe (Malumbres, 2014). Unlike other CDKs, activation-segment phosphorylation by CAK is not required; binding of p35/p39 alone induces the active conformation (Dhariwala & Rajadhyaksha, 2008). A glycine-rich loop positions ATP, and a cyclin-box–like interface accommodates p35/p39, replacing classical cyclins (Su & Tsai, 2011). Inhibitory phosphorylation sites common in cell-cycle CDKs are absent or functionally altered (Malumbres, 2014).

## Regulation

• Activation by tight binding to p35 or p39 provides spatial and temporal control in post-mitotic neurons (Su & Tsai, 2011).  
• Calpain-mediated cleavage of p35 generates p25, which forms a hyper-stable complex with CDK5, prolonging activity and contributing to neurodegeneration (Dhariwala & Rajadhyaksha, 2008; Mapelli et al., 2005).  
• CDK5 autophosphorylates p35, promoting its turnover and establishing negative feedback (Dhariwala & Rajadhyaksha, 2008).  
• Additional modulation arises from interactions with proteins such as p53, HDAC1 and small GTPases, integrating stress and developmental signals (Cheung & Ip, 2012; Łukasik et al., 2021).

## Function

Highly expressed in neurons, CDK5 governs neuronal migration, neurite outgrowth, axon guidance, synaptogenesis and synaptic plasticity via phosphorylation of cytoskeletal and vesicle-cycling proteins (Dhariwala & Rajadhyaksha, 2008; Su & Tsai, 2011). It also:  
• Regulates neurotransmitter release through synapsin-1, dynamin-1, amphiphysin and synaptojanin-1 (Peyressatre et al., 2015).  
• Controls endothelial cell migration and angiogenesis by affecting Rac1-dependent lamellipodia formation (Liebl et al., 2010).  
• Stabilises p53 under genotoxic stress, linking CDK5 to apoptosis (Dhariwala & Rajadhyaksha, 2008).  
• Modulates circadian rhythms via phosphorylation of CLOCK (Dhariwala & Rajadhyaksha, 2008).  
Its interactome includes vimentin, paxillin and multiple small GTPases, highlighting roles beyond the nervous system (Łukasik et al., 2021).

## Inhibitors

The ATP-competitive inhibitor roscovitine (also known as seliciclib) is widely used experimentally to inhibit CDK5 activity (Peyressatre et al., 2015).

## Other Comments

Hyperactivation of CDK5—particularly through p25 formation—is implicated in Alzheimer’s, Parkinson’s and ALS, making the kinase a therapeutic target (Cheung & Ip, 2012; Dhariwala & Rajadhyaksha, 2008). Dysregulated activity can drive aberrant neuronal cell-cycle re-entry and apoptosis, and emerging proteomic data suggest additional roles in cancer cell migration and proliferation (Xu et al., 2014; Łukasik et al., 2021).

## References

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